



NATIONAL PBM BULLETIN

August 6, 2013

DEPARTMENT OF VETERANS AFFAIRS VETERANS HEALTH ADMINISTRATION (VHA)
PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP),
CENTER FOR MEDICATION SAFETY (VA MEDSAFE), AND WOMEN'S HEALTH SERVICES

VALPROATE ANTI-SEIZURE PRODUCTS AND CONTRAINDICATION FOR MIGRAINE PREVENTION IN PREGNANT WOMEN DUE TO DECREASED IQ SCORES IN EXPOSED CHILDREN

I. ISSUE

New Drug Labeling Information for Valproate Products:

- Valproate products are contraindicated during pregnancy for prevention of migraine headaches (FDA Pregnancy category X).
- During pregnancy, the benefits of valproate may outweigh the risks when used for treatment of epilepsy or bipolar disorder if other treatments have failed to provide adequate symptom control or are otherwise unacceptable. (FDA Pregnancy Category D).

II. BACKGROUND

On May 6, 2013, the U.S. Food and Drug Administration issued a drug safety communication announcing a contraindication to the use of valproate medications during pregnancy when the medication is used to prevent migraine headaches. This labeling change is based on final results from a study that demonstrated lower IQ scores for children at age 6 years who were exposed to valproate during pregnancy compared to the IQ scores of children exposed to another anti-seizure medication during pregnancy. Valproate products include: valproate sodium (Depacon), divalproex sodium (Depakote, Depakote CP, and Depakote ER), valproic acid (Depakene and Stavzor), and their generics. Out of approximately 1700 female veterans of childbearing age on valproate identified within the VA system nation-wide (as of the second quarter in fiscal year 2013), 40% had a diagnosis for migraines, while more than 75% had a diagnosis for bipolar disorder and almost 7% had epilepsy (groups not mutually exclusive).

III. DISCUSSION

All pregnancies have a background risk of birth defects (about 3%), pregnancy loss (about 15%), or other adverse outcomes regardless of drug exposure. Children exposed to a valproate medication during pregnancy have a 4-fold higher risk for having a major congenital malformation than children exposed to another anti-epileptic medication during pregnancy. Maternal valproate use during pregnancy increases a child's risk for:

- **Decreased cognitive function (IQ)** at age 6 years compared to children exposed to a different anti-epileptic medication during pregnancy (8 to 11 points lower).¹
- **Neural tube defects (NTDs)** - There is a four-fold increased risk for NTDs compared to babies exposed to another anti-seizure medication during pregnancy. The risk is 1 to 2 out of 100 exposed births, compared to a general population risk for NTDs of about 7 per 10,000 births.
- **Other congenital malformations** including cardiovascular and craniofacial malformations.

IV. PROVIDER RECOMMENDATIONS

When prescribing valproate for a woman of childbearing age:

- Consider the pregnancy-associated risks of her medical condition, if untreated or undertreated, as well as the pregnancy-associated risks of the medication used to treat her condition.
 - Seizures place a pregnant woman and her fetus at risk of injury due to hypoxia, falls, and motor vehicle accidents if she seizes while driving.
 - Mood disorders are associated with an increase in risk-taking behaviors including substance use, decreased compliance with and late entry into prenatal care, and suicidality.

When counseling a woman of childbearing age regarding use of valproate:

- Counsel women about the increased risk for decreased IQ in children exposed to valproate products during pregnancy.
- Counsel women using valproate about the increased risk of other major structural and functional birth defects, particularly neural

tube defects, when valproate is used during pregnancy.

- Counsel women who *are not planning a pregnancy* about using highly effective contraception (e.g., IUD, hormone implant). Information about effectiveness and features of different contraceptive methods can be found under “Information Sheets and Resources” on the Women’s Reproductive Health SharePoint site: <http://vaww.infoshare.va.gov/sites/womenshealth/reproductive/resources/default.aspx>
- Counsel women using valproate who *are considering a pregnancy* about the risks and benefits of valproate use during pregnancy and alternative therapeutic options based on their medical condition and clinical needs.
- For women who require medication for migraine prophylaxis, discuss valproate’s contraindication during pregnancy and review alternative treatments and their pregnancy associated risks (e.g. use of beta blockers require additional monitoring for reduced fetal growth).
- All women of childbearing age should have 0.4 to 1 mg of folate per day from dietary sources and/or vitamin supplementation to reduce the risk for neural tube defects should pregnancy occur. Women taking valproate are at increased risk of neural tube defects and should increase folate intake to 4 mg daily prior to conception and during pregnancy. The following foods are high in folic acid: lentils, beans (pinto, black, navy, kidney, lima, black-eyed peas), spinach, turnip and collard greens, fortified breakfast cereals, white rice, asparagus, spaghetti, and brussel sprouts.
- Inform pregnant women taking valproate products about the North American Antiepileptic Drug (NAAED) Pregnancy Registry, which collects data on pregnant exposures to valproate and other anti-epileptic medications. Patients can enroll by calling toll free: 1-888-233-2334. Information on the registry can be found at: <http://www.aedpregnancyregistry.org/>.
- Providers should continue to report any adverse reactions with the use of valproate products (brand and generic valproate sodium, divalproex sodium, and valproic acid) by entering the information into CPRS’ Allergies/ Adverse Reactions field and/or via local reporting mechanisms. Adverse events should also be reported, as appropriate, to the VA ADERS program and FDA MedWatch (1-800-FDA-1088, fax 1-800-FDA-0178, online at <https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm>, or by mail).

V. REFERENCES

1. Meador KJ, Baker GA, Browning N, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurology* 2013; 12 (3): 244-252.
2. FDA Drug Safety Communication: Valproate Anti-seizure Products Contraindicated for Migraine Prevention in Pregnant Women due to Decreased IQ Scores in Exposed Children. <http://www.fda.gov/Drugs/DrugSafety/ucm350684.htm> . (Accessed 05/06/2013).

VI. RESOURCES

1. **Information about reproductive risks of medications:**
 - a. **REPROTOX™** – an online database of reproductive risk information for medications and chemicals. The VA national subscription provides free access for all VA employees at: <http://va.reprotox.us>
 - b. **FDA approved full prescribing information**
 - Drugs@FDA (search by drug name or active ingredient): <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>
 - DailyMed (may have prescribing information for older medications that are no longer available at the Drugs@FDA site): <http://dailymed.nlm.nih.gov/>
 - Drug manufacturer websites for individual medications
2. **Valproate Use During Pregnancy FAQ and Contraceptive Method Effectiveness and Features:** <http://vaww.infoshare.va.gov/sites/womenshealth/reproductive/resources/default.aspx>
3. **Pregnancy registry for women taking valproate medications during pregnancy:** North American Anti-Epileptic Drug Pregnancy Registry - <http://www.aedpregnancyregistry.org/>. Patients can enroll by calling toll free: 1-888-233-2334.

ACTIONS

- **Facility Director** (or physician designee): Forward this document to the Facility Chief of Staff (COS).
- **Facility COS and Chief Nurse Executives:** Forward this document to all appropriate providers who prescribe these medications (e.g., **primary care providers, neurologists, mental health providers, and women’s health providers, including contract providers, etc.**). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.
- **ACOS for R&D:** Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).